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REVIEW ARTICLE

The CD39-adenosinergic axis in the pathogenesis of renal ischemia–reperfusion injury

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Abstract Hypoxic injury occurs when the blood supply to an organ is interrupted; subsequent reperfusion halts ongoing ischemic damage but paradoxically leads to further inflammation. Together this is termed ischemia–reperfusion injury (IRI). IRI is inherent to organ transplantation and impacts both the short- and long-term outcomes of the transplanted organ. Activation of the purinergic signalling pathway is intrinsic to the pathogenesis of, and endogenous response to IRI. Therapies targeting the purinergic pathway in IRI are an attractive avenue for the improvement of transplant outcomes and the basis of ongoing research. This review aims to examine the role of adenosine receptor signalling and the ecto-nucleotidases, CD39 and CD73, in IRI, with a particular focus on renal IRI.

Keywords Ischemia–reperfusion injury · Renal transplant · Purinergic signalling · Adenosine receptor · Ectonucleotidase

Abbreviations

ADO	Adenosine
ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
ATP	Adenosine triphosphate
cAMP	3′-5′-Cyclic adenosine monophosphate
EC	Endothelial cells
ENT1	Equilibrative nucleoside transporter 1
HIF	Hypoxia inducible factor
IP	Ischemic preconditioning
IRI	Ischemia–reperfusion injury
NPP	Nucleotide pyrophosphatase/phosphodiesterase
PD-1	Programmed death-1
PTC	Proximal tubule cells
$S1P_1R$	Sphingosine-1-phosphate receptors
SK-1	Sphingosine kinase-1
Treg	Regulatory T cells

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Ischemia–reperfusion injury (IRI) is an obligatory insult in transplantation occurring at the time of organ procurement and engraftment. Ischemia is induced when blood flow to an organ is interrupted. Re-establishment of blood flow is essential to prevent ongoing hypoxic injury but paradoxically imparts further injury, termed IRI. Warm ischemia is relatively short in brain dead donors (<30 min); however, this can be prolonged in donors following cardiac arrest (up to 90 min). Furthermore, unique to transplantation is the period of cold preservation, which slows the cellular metabolic rate in order to minimize ongoing ischemic damage but which may be prolonged (extending to hours). The clinical ramifications of IRI include systemic inflammatory effects and organ dysfunction, increasing graft immunogenicity, the risk of delayed graft function, acute rejection, and chronic allograft dysfunction.

There is substantial evidence implicating purinergic signalling in both the pathogenesis of and the endogenous response to IRI, and strategies targeting various aspects of the pathway may therefore be of therapeutic potential. ATP, present in relatively high concentrations intracellularly, is extruded from injured and necrotic cells into the extracellular space or released in a more controlled manner from apoptotic cells through pannexin hemi-channels and from inflammatory cells via connexin hemi-channels [1]. Upon release, extracellular ATP acts in an autocrine or paracrine manner on specific cell-surface P2 receptors belonging to two subclasses, the G protein-coupled P2Y receptors and the ATP-gated P2X nonselective cation channels [2]. ATP

promotes inflammation in IRI via P2X7 [3] signalling, $P2Y_6$ upregulation [4], and activation of the NOD-like receptor pyrin domain containing 3 (Nlrp3) inflammasone [5], and acts as a chemoattractant [6]. P2 receptor-mediated signals are quickly terminated by scavenging of ATP by cell-surface ecto-nucleotidases. Four membrane-bound ectonucleotidases have been characterized, namely NTPDase 1 (CD39), NTPDase 2 (CD39L1), NTPDase 3, and NTPDase 4. The subtypes can be differentiated according to substrate preference: CD39 hydrolyzes ATP and ADP equally to AMP; CD39L1 preferentially hydrolyzes ADP, whereas NTPDase 3 and 8 preferentially hydrolyze ATP [7]. Within the renal cortex, CD39 is expressed on vascular smooth muscle cells and vascular endothelium of interlobular arteries, afferent glomerular arterioles and peritubular capillaries, whereas CD39L1 is expressed in Bowman's capsule, glomerular arterioles, adventitia of blood vessels, and pelvic wall [8]. The nucleotide pyrophosphatase/phosphodiesterase (NPP) family are ectonucleotidases that can also metabolize ATP directly to ADP and AMP [9]. NPP1–3 are widely distributed in most tissues, and NPP1 is distributed in the renal convoluted tubules and endothelial cells [10]. Adenosine generated by the activation of the ectonucleotidases activates P1 receptors identified as A_1, A_{2A}, A_{2B}, and A_3 receptors [2] and mitigates ongoing injury. A_1R and A_3R are coupled to the G-inhibitory subunit which leads to reduction in intracellular cAMP upon activation. The A_{2A} and A_{2B} receptors are coupled to the G-stimulatory subunit resulting in an increase in intracellular cAMP. The role of CD39, CD73, and the adenosine receptors in ischemia–reperfusion injury will be presented in this review, with the major focus on renal IRI (Fig. 1).

Adenosine signalling in IRI

Adenosine is an endogenous autocrine anti-inflammatory molecule normally found in very low levels in the extracellular space. In the kidney, adenosine regulates renin release, glomerular filtration rate, and renal vascular tone and is a critical regulator of tubular glomerular feedback (reviewed in [11]). Under hypoxic conditions, the pericellular concentration of adenosine rises dramatically due to hydrolysis of nucleotides (released from injured or dying cells) by the enzymes CD39 and CD73. All four adenosine receptors are expressed within the kidney on various cell types and locations [11], and adenosine receptor levels are increased at the transcriptional level under ischemic conditions, implicating adenosine signalling in tissue adaptation to hypoxia (reviewed in [12]). Indeed, adenosine is a key mediator of ischemic preconditioning (IP) [13], a process where short periods of ischemia followed by reperfusion renders the organ refractory to further ischemia-induced dysfunction.

Adenosine 1 receptor (A_1R)

Renal A_1R expression is predominantly in the distal afferent arteriole, mesangial cells, proximal convoluted tubules, medullary collecting ducts, and papillary surface epithelia [14]. A_1R activation ameliorates ischemic-induced acute kidney injury [15] with reduced apoptosis, necrosis, and inflammation [16]. In keeping with this, wild-type mice treated with an A_1R antagonist or mice deficient in A_1R exhibit worse renal injury after 30 min ischemia and 24 h reperfusion [17] mediated by increased nuclear translocation of hypoxia-inducible factor 1α (HIF-1α) and induction of sphingosine kinase-1 (SK1) in the proximal tubule [18]. Kidney-specific protection was induced using the A_1R allosteric enhancer PD-81723, which binds to a site on the A_1R that is distinct from the adenosine binding site and augments the adenosine–A_1R interaction. Both SK1 and sphingosine-1-phosphate receptors ($S1P_1R$) in the proximal tubule are critical in mediating this effect [19]. In contrast to IRI, cisplatin- [20] and radiocontrast-induced [21] kidney injury is mediated by activation of the A_1R, and inhibition of the A_1R ameliorates injury in these models. These data highlight the complex and context-dependent outcomes of adenosine receptor signalling within the kidney.

In a model of stroke, animals treated with the A_1R agonist 2-chloro-*N*(6)-cyclopentyladenosine showed reduced neurological deficit scores following 2 h occlusion of the middle cerebral artery. Hind limb remote IP conferred neuroprotection, which was abolished by the A_1R antagonist 8-cyclopentyl-1,3-dipropylxanthine [22].

Adenosine 2A receptor ($A_{2A}R$)

$A_{2A}R$ in the kidney is located predominantly in the glomerular epithelium and adjacent vasculature [14], and $A_{2A}R$ activation increases blood flow to the renal medulla. The $A_{2A}R$ is also expressed on $CD4^+$ T cells and is involved in the termination of T cell proliferation [23], playing a critical role in the physiological regulation of immune responses in vivo (reviewed in [24]). Activation of the $A_{2A}R$ by the stable agonist ATL146e mediated protection against renal IRI, an effect that was localized to circulating IFNγ-producing $CD4^+$ T cells [25]. Similarly, the infarct-sparing effect of $A_{2A}R$ activation in a model of myocardial ischemia was due to inhibition of $CD4^+$ T cell accumulation [26]. Interestingly, in liver IRI, ATL146e potently inhibits the $CD4^+$ subset of IFNγ-producing NKT cells, mitigating injury [27].

Adenosine 2B receptor ($A_{2B}R$)

Whereas the protective effect of $A_{2A}R$ activation in renal IRI operates predominantly via circulating cells, the site of

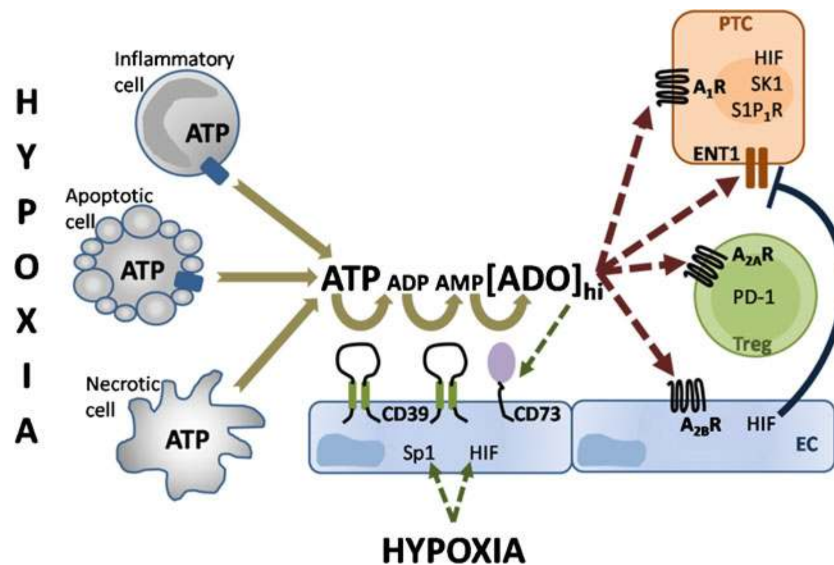

Fig. 1 Mechanism of protection by adenosine in renal IRI. In IRI, ATP is released from inflammatory and apoptotic cells via connexin and pannexin hemi-channels (*blue rectangle*) or directly from necrotic cells into the extracellular space. ATP is converted through an enzymatic process by CD39 and CD73 on endothelial cells (EC) to adenosine (ADO), increasing its extracellular concentration ($[ADO]_{hi}$). Under hypoxic conditions, CD39 is upregulated by hypoxia-inducible specificity protein 1 (Sp1) and CD73 by hypoxia-inducible factor (HIF). Adenosine mediates its anti-inflammatory effects (*brown broken arrows*) via A_1R on proximal tubule cells (PTC), $A_{2A}R$ on T regulatory cells (Treg) and $A_{2B}R$ on endothelial cells (EC). Adenosine itself increases the expression of CD73 (*single green broken arrow*). During ischemia, hypoxia-inducible factor is activated which inhibits transcription of equilibrative nucleoside transporter 1 (ENT1) enabling adenosine to remain in the extracellular space. HIF also increases the expression of A_1R and $A_{2B}R$. Sphingosine kinase-1 (SK1) and sphingosine-1-phosphate receptors ($S1P_1R$) in the PTC augment the adenosine–A_1R interaction. In the Treg, $A_{2A}R$ activation increases the expression of protein programmed-death 1(PD-1) which suppresses innate immune responses

action of protection mediated by $A_{2B}R$ activation is the renal parenchyma [28]. The $A_{2B}R$ is expressed predominantly in the renal vasculature with little expression in the renal epithelia and is upregulated following 60 min of ischemia [29]. Activation of this receptor by the agonist BAY 60–6583 lessened injury following 45 min of renal ischemia. During hypoxia, the equilibrative nucleoside transporter 1 (ENT1) is markedly upregulated in the renal tubules and allows for the passive flow of extracellular adenosine into the intracellular compartment. Inhibition of ENT1 with dipyridamole led to sustained levels of extracellular adenosine, protecting against IRI. The protective effect persisted in mice in which $A_{2B}R$ expression was deleted in the renal tubular epithelia but was lost in those where $A_{2B}R$ expression was selectively knocked out in the renal vasculature [29].

$A_{2B}R$ activation is critical for protection against renal IRI by IP. Using a hanging weight system for repeated occlusion and release of the renal artery, Grenz et al. demonstrated that four cycles of ischemia–reperfusion (4 min each) protected against a subsequent period of 45 min of renal ischemia. The IP increased renal adenosine content, and $A_{2B}R$ was selectively upregulated at the transcriptional level 60 min after IP. Furthermore, IP was associated with reduced expression of tumor necrosis factor α (TNFα) and interleukin-6 (IL-6) and increased expression of interleukin-10 (IL-10); nuclear factor kappa-light-chain-enhancer of activated B cells (NF−κB) activity was reduced, and the activity of its inhibitor IκBα was increased. The effects of IP were abolished in mice deficient in the $A_{2B}R$ or by pre-treatment of wild-type mice with the $A_{2B}R$ antagonist PSB1115 [28].

In the liver, $A_{2B}R$ mRNA is the most abundant of all adenosine receptor subtypes. Recently, the $A_{2B}R$ has been implicated in liver protection conferred by hypoxic preconditioning where mice breathe 10 % oxygen for 10 min followed by 10 min of 21 % oxygen before 45 min of left lobe liver ischemia and 4 h reperfusion. Liver injury and the expression of IL-6 and TNFα were increased in mice in which the $A_{2B}R$ was deleted [30].

HIF-1α is central in coordinating the purinergic response to hypoxia. A functional binding site for HIF-1α within the promoter of the $A_{2B}R$ is essential for induction of the receptor under hypoxic conditions, and $A_{2B}R$ expression is significantly decreased in HIF-1α mutant mice [31]. Furthermore, HIF-1α upregulates CD73 [32] (see below) and represses ENT1 [33], which together serve to increase the pericellular concentration of adenosine. HIF-1α activation with dimethyloxallyl glycine induced CD73 and $A_{2B}R$ transcript and protein expression and attenuated intestinal IRI [34]. HIF-1α-dependent upregulation of the $A_{2B}R$ on dendritic cells occurs during hypoxia, and antagonism of the $A_{2B}R$ increases the production of interleukin-12 (IL-12p70), TNF-α, and interferon-gamma (IFNγ) [35].

Treatment with the $A_{2B}R$ agonist BAY 60–6583 reduced infarct size in cardiac IRI [36]. The target of $A_{2B}R$ activation was shown to be the *Per2* gene, a circadian rhythm protein (period circadian protein homolog 2) which enhanced the glycolytic capacity of the ischemic heart through HIF-1α [37]. Further studies have shown that $A_{2B}R$ signalling on bone marrow-derived cells conferred protection against IRI manifesting as a decrease in infarct size [38], although others have demonstrated an essential and additional role for the $A_{2A}R$ in mitigating cardiac injury [39].

Adenosine 3 receptor (A_3R)

The precise location of the A_3R within the kidney has not been defined [40], and manipulation of the A_3R has been shown to either exacerbate or protect against renal IRI. In rats, the selective activation or inhibition of the A_3R worsened or attenuated renal IRI, respectively [15]. Consistent with this, mice deficient in A_3R or wild-type mice pretreated with A_3R antagonist were protected from renal IRI [41].

The role of ectonucleotidases in IRI

ENTPDase 1 (CD39) and 5′-ectonucleotidase (CD73)

CD39 is the major generator of extracellular adenosine in experimental IRI, and deletion of CD39 enhances susceptibility to hypoxic injury in the kidney [42, 43], liver [44], heart [45], and intestine [46] (Table 1). In the kidney, CD39 is upregulated threefold at the transcript level 90 min after IP compared with controls, whereas transcriptional levels of NTPDase 2 and 3 remain unchanged after IP [47]. The increase in CD39 transcript and protein levels is associated with an increase in the adenosine tissue content up to ninefold higher than the baseline level [47]. Consistent with this, protection against renal IRI could not be induced following IP in CD39KO mice or with administration of sodium polyoxotungstate (POM-1), which inhibits E-NTPDase activity. Similarly, following IP in the liver and heart, CD39 expression was induced at the transcript and protein levels and associated with improved outcomes. The upregulation of CD39 was dependent on Sp1 (specificity protein1), a ubiquitously expressed transcription factor implicated in promoting hypoxic gene transcription [45, 48].

Administration of apyrase, a soluble form of CD39, abolished IRI irrespective of IP in the kidney [47], heart [45], liver [44, 48], and intestine [46] by increasing tissue adenosine content and removing proinflammatory nucleotides. Similarly, mice that over-expressed CD39 [49] were protected from renal IRI [42, 43, 50] including that in a syngeneic renal transplant model encompassing extended cold preservation [42]. More recently, protection against cardiac ischemia has been demonstrated in mice over-expressing CD39, through an $A_{2B}R$-dependent mechanism [51]. Such protection was also observed in pigs over-expressing CD39 [52]. In a liver transplant model characterized by extended cold preservation, mice recipient of CD39 over-expressing liver grafts have less hepatic injury as evidenced by lower serum alanine aminotransferase and histological scores [53]. The mechanism of protection in this model was due to an associated hepatic $CD4^+$ T cell lymphopenia rather than the tissue restricted expression of CD39 (Table 1).

CD39 is expressed on microparticles, which are phospholipid vesicles derived from activated platelets, leukocytes, or endothelial cells. Co-incubation of microparticles from wild-type mice with liver sinusoidal endothelial cells (LSEC) decreased lipopolysaccharide-induced IL-6 and TNFα release from the LSEC. However, this effect was lost with when microparticles from *Cd39*-null mice were used, suggesting an anti-inflammatory role for CD39 on microparticles in modulating vascular signals in the liver [54].

Table 1 The impact of CD39 in animal models of ischemia–reperfusion injury

Animal model of IRI		Impact of CD39 on injury after IRI		
		Cd39 null	CD39 over-expression	Apyrase
Renal	Warm IRI in mice [43, 47, 50]	Severe injury	Protective	Protective
	Transplantation in mice with cold IRI [42]	Severe injury	Protective	Protective
Heart	Warm IRI in mice [45, 101]	Severe injury	N/A	Protective
	Warm IRI in swine [52]	Severe injury	Protective	N/A
Liver	Warm IRI in mice [44, 48]	Severe injury	N/A	Protective
	Transplantation in mice with cold IRI [53]	N/A	Protective	N/A
Intestine	Warm IRI in mice [46]	Severe injury	N/A	Protective
Lung	Syngeneic transplantation in rats with cold IRI [102]	N/A	N/A	Protective

N/A data not available

Recently, microparticles released from endothelial progenitor cells were shown to mediate protection in a model of renal IRI through miRNA 296 and 126 induced vascular regeneration [55]. The involvement of CD39-expressing microparticles in the amelioration of IRI is yet to be examined.

CD73 plays an important role in the vascular adaptation to hypoxia [56], and mice deficient in CD73 have a pro-inflammatory phenotype with increased VCAM-1 expression on endothelial cells and heightened susceptibility to vascular inflammation and neointima formation [57]. CD73 activity attenuates hypoxia-induced vascular leakage, FMLP (formyl-Met-Leu-Phe-OH)-stimulated neutrophil adhesion to endothelial cells, and neutrophil accumulation in tissues [58, 59]. When co-incubated with endothelial cells, neutrophils release micromolar concentrations of 5′-AMP that is rapidly converted by surface-bound CD73 to adenosine, which interacts directly with endothelial-associated $A_{2B}R$ [60].

CD73 is transcriptionally upregulated by renal IP, its activity increasing 2.5-fold within 30 min [61]. In the absence of CD73, IP did not increase tissue adenosine content, and mice remained susceptible to 30 min of renal ischemia. Protection following IP was restored in CD73-deficient mice by reconstitution with soluble 5′ ectonucleotidase, and wild-type mice treated with this molecule were protected regardless of IP [61]. CD73 is also upregulated at the transcriptional and protein level following hepatic IP, and IP does not protect against hepatic IRI in mice deficient in CD73 [62]. CD73 upregulation following IP is HIF-1α-dependent, at least in the gut and heart [34, 36].

CD73 expression is also increased at the mRNA and protein level by the stable adenosine agonist NECA. This correlated with an increase in CD73 functional activity and was mediated predominantly via activation of the $A_{2B}R$ [63]. The CD73 promoter contains a cAMP response element, thus linking adenosine signalling via the $A_{2B}R$ with upregulation of CD73. CD73 expression and activity is also modulated by exposure to interferon-β (IFN-β) [64]. Acute lung injury, as a systemic complication of intestinal IRI, was reduced by 90 % following IFN-β pre-treatment. A 230 % increase in CD73 activity in the lungs of these mice was demonstrated, although interestingly the level of intestinal damage was not altered [64].

The impact of CD73 deficiency in renal IRI is variable. Using a model employing 45 min of renal ischemia and 24 h of reperfusion, Jian et al. demonstrated more severe injury in CD73-deficient mice manifesting in necrosis, congestion, and a marked inflammatory infiltrate. Some injury was evident within the kidneys of wild-type mice, with edema, congestion, and aggregates of inflammatory cells; however, neither serum creatinine nor tubular injury score was reported for either group [65]. Grenz et al. demonstrated severe injury in CD73-deficient mice equivalent to that of wild-type following 30 min of ischemia and 24 h reperfusion [61]. In contrast, CD73 deficiency was protective in a less severe model of renal IRI involving right nephrectomy, occlusion of the left renal pedicle for 18 min, and 24 h of reperfusion [49]. CD73-deficient mice had a lower serum creatinine level and reduced tubular injury score. Furthermore, reconstitution of CD73-deficient mice with soluble CD73 restored injury, and wild-type mice pre-treated with CD73 inhibitor were protected. We speculate that the accumulation of extracellular AMP could exert a protective effect in mild renal IRI, possibly via the A_1R given the recent identification of AMP as a ligand for this receptor [66].

CD39 and CD73 are highly efficient enzymes; CD39, for example, has a catalytic efficiency (kcat/Km) for ATP and ADP of 2.0×10^7 and 1.4×10^7 min/M, respectively [67]. The rate at which ATP is scavenged and converted to adenosine in the setting of IRI will depend on several factors, including the basal and hypoxia-induced expression levels of CD39 and CD73.

Cellular expression of ectonucleotidases in IRI

T cells form an important connection between the innate and adaptive arms of the immune response to IRI [68]. Mice deficient in T cells are protected from IRI [69], and the adoptive transfer of T cells restores injury. Specific subpopulations of $CD4^+$ and $CD8^+$ T cells have been shown to mediate injury in models of brain [70], heart [26], and kidney [25] IRI. Th1 cells producing IFNγ are deleterious, but IL4-producing Th2 cells are protective in renal IRI [71, 72], while IL-17 produced by γδ T cells underpins cerebral IRI [73].

CD39 and CD73 expression on circulating and resident cardiac leukocytes and coronary endothelial cells has been examined under basal conditions and following IRI [74]. Under basal conditions, CD39 was expressed by all resident and circulating immune cells, being highest on myeloid cells and included antigen presenting cells (APCs). Coronary endothelial cells also expressed CD39 at high levels, whereas CD73 expression was mainly restricted to T cells. Following 50 min of cardiac ischemia (induced via occlusion of the left anterior descending artery), the total number of immune cells increased dramatically and were mainly granulocytes expressing both CD39 and CD73. It was suggested that CD39-expressing APCs perform a sentinel function in cardiac protection by hydrolyzing ATP. CD73 upregulated by resident and infiltrating lymphoid cells favors the local generation of adenosine.

CD39 and CD73 are co-expressed on mouse regulatory T cells (Treg) [23, 75, 76], and the $A_{2A}R$ is the most highly

expressed adenosine receptor subtype in Treg at the mRNA level [77]. Treg suppress innate inflammation associated with IRI: Depletion of Treg exacerbated renal IRI [78] and depletion of IL-10-specific Treg exacerbated cerebral injury [79]. IP increased Treg, reducing injury [80], and the transfer of Treg post-IRI accelerated recovery [81]. Previous work has demonstrated that activation of the $A_{2A}R$ on $CD4^+$ T cells mitigated renal IRI [25] (see above). This has been further defined to $A_{2A}R$ activation on Treg, which enhanced the expression of the membrane protein programmed death-1 (PD-1) and suppressed kidney IRI [77]. Adoptive transfer of Treg from CD73KO mice offered significantly less protection from renal IRI compared with wild-type Treg, suggesting that adenosine generated by Treg is important in reducing injury. Surprisingly, the transfer of wild-type Treg conferred protection in A_{2A}RKO hosts, implicating a minimal effect of activation of host $A_{2A}R$. However, transfer of Treg from A_{2A}RKO mice did not modify renal IRI, demonstrating that protection mediated by Treg required activation of the $A_{2A}R$ on the Treg itself [69].

Clinical application

The protection against IRI by adenosine and its analogues experimentally has led to trials examining the effectiveness of adenosine clinically. In a meta-analysis, intracoronary adenosine administered to patients with acute myocardial infarction undergoing percutaneous coronary intervention improved electrocardiographic outcomes with a trend to less major adverse cardiac events, heart failure, and cardiovascular mortality [82]. However, adenosine given during coronary artery bypass graft surgery did not confer benefit [83]. Acadesine, an adenosine-regulating agent which increases both intracellular and extracellular adenosine, has been examined in a number of studies [84–86]. In a meta-analysis, acadesine therapy correlated with a reduction in perioperative myocardial infarction, cardiac death at day 4, and the composite of cardiac death, stroke, and myocardial infarction [87]. However, in a subsequent randomized controlled trial, acadesine had no effect on all-cause mortality, non-fatal stroke, and severe left ventricular dysfunction following coronary artery bypass surgery [88].

Adenosine at a concentration of 5 μM is a constituent of University of Wisconsin (UW) organ preservation solution. Compared with Celsior preservation solution, UW is associated with less ischemic necrosis in early cardiac allograft biopsies [89] and improved short-term outcomes [90]. UW was superior to histidine-tryptophan-ketoglutarate (HTK) solution after prolonged cold preservation of renal grafts [91] but inferior to Celsior in liver transplantation associated with more post-reperfusion syndrome [92]. Adenosine-lidocaine preservation solution supplemented with melatonin and insulin improved cardiac output, heart rate, and blood pressure following cold storage of rat hearts for 8 h. Adenosine-lidocaine alone was more efficacious than Custodial HTK and Celsior preservation solutions [93]. The same group showed that rewarming rat hearts after 6 h of cold static storage in adenosine-lidocaine solution improved aortic flow rate, coronary flow, and cardiac output [94].

Remote ischemic preconditioning, consisting of repeated episodes of ischemia and reperfusion in a remote organ, protects against renal and cardiac IRI through a number of neuronal, humoral, and systemic factors (reviewed in [95]). Adenosine levels are elevated by remote IP and inhibition of adenosine signalling abolishes protection [96, 97]. The $A_{2B}R$ predominates in cardiac protection mediated by remote IP [98]. Clinically, remote IP prevents contrast nephropathy in high-risk patients undergoing coronary angiogram [99]. Furthermore, in patients undergoing abdominal aortic vascular repair, the incidence of acute renal impairment was also reduced after remote IP in the left arm [100]. A randomized double-blind placebo-controlled trial of 400 living-donor renal transplant patients investigating remote IP in renal transplantation ("Renal protection against ischemia–reperfusion in transplantation, REPAIR") is currently underway (ClinicalTrials.gov identifier: ISRCTN30083294).

Conclusion

Adenosine receptors are ubiquitously expressed in the renal vasculature and parenchyma. Targeted therapies towards the purinergic pathway have shown promising results in animal studies and are potential therapeutic tools in reduction of ischemic–reperfusion injury, particularly following renal transplantation.

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